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PRINCIPAL INVESTIGATOR: Kimberly A. Khalsa

CONTRACTING ORGANIZATION: The University of Michigan
Ann Arbor, MI 48109-1274

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Kimberly A. Khalsa
Jeffery A. Fessler

kkhalsa@umich.edu

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14. ABSTRACT

The overall goal of this project is to develop, implement, and evaluate methods for improving image quality in dynamic MR imaging. We focus specifically on dynamic contrast-enhanced (DCE) imaging of breast cancer patients. We explore reconstruction methods that use explicit temporal models in object space. Simulation and phantom studies have indicated that our algorithms produce quality reconstructed image sequences that exhibit both high spatial and high temporal resolution.

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1 Introduction

The overall goal of this project is to develop, implement, and evaluate methods for improving image quality in dynamic magnetic resonance imaging. We focus specifically on dynamic contrast-enhanced (DCE) imaging of breast cancer patients. The fundamental challenge in dynamic MRI is the tradeoff between spatial resolution and temporal resolution. In addressing this problem, most traditional dynamic acquisition methods and associated reconstruction methods have been based on operations in the data domain, known as k-space, implicitly assuming that the object varies smoothly in time. We explore reconstruction methods that instead use explicit temporal models in object space. We develop iterative methods for fitting these models to the measured k-space data using regularized estimators without attempting to synthesize any of the 'missing' k-space data. We hypothesize that DCE-MRI quality can be improved using our proposed reconstruction scheme which includes explicit temporal regularization in object space.

2 Body

2.1 Reconstruction Model and Cost Function Design

Our proposed method for reconstructing DCE MR images is based on minimizing a three term image domain cost function. We call our method Temporal Regularization Use in Image Reconstruction (TRUIR). The first term in the cost function is a data fidelity term, which ensures that the image estimate is consistent with the measured data. The second and third terms in the cost function are weighted spatial and temporal penalty terms. We use these terms to incorporate our *a priori* knowledge about the object, namely that there is a certain smoothness expected in both space and time. The spatial regularizer penalizes large differences between neighboring pixels in space and the temporal regularizer penalizes large differences between neighboring pixels in time. There are regularization parameters α and β that determine the relative weighting within the cost function of the spatial and temporal regularization terms, respectively.

In the past decade the idea of using multiple receiver coils to simultaneously acquire MR data has been introduced and the practice is now widespread [1–3]. This is known as *parallel imaging* and, in general, reduces the required scan time. Therefore we deemed it important to incorporate parallel imaging into our methods and have done so.

In addition to the work discussed in the following sections, this year we have added many tools and functions to the group's code base, including the creation of a new data object to assist in TRUIR reconstructions. These additions will be available to fellow and future students and researchers, which will help ensure the long-term progress and viability of this project.

2.2 Choice of Regularization Parameters

A challenging aspect of any regularized formulation is choosing appropriate regularization terms, as well as determining the relative weights of these terms. In our formulation, the weighting of these terms is implemented with temporal and spatial regularization parameters, α and β. Regularization parameter choice can significantly influence the quality of the reconstructed images. For practical use of our reconstruction approach, one must understand how the regularization parameters α and β in the cost function affect the reconstructed images. For TRUIR reconstruction of dynamic image sequences, the temporal regularization parameter α is of particular importance. Essentially we want to use an α that is large enough to provide adequate "connectivity" between the frames, but small enough so that the reconstructed image sequence correctly reflects dynamic changes in the object.

We aimed to address the issue of regularization parameter choice by analyzing the resolution properties of the TRUIR method. To do this, we are examining the local impulse response in space and time. Our initial evalution looked at the spatial and temporal resolution of a TRUIR formulation for a single coil acquisition and found an expected relationship between β and spatial resolution, and α and temporal resolution [4]. Similar analysis of penalized-likelihood reconstruction for (static) tomography was presented in [5]. We are now evaluating the effects of the regularization parameter choice on the full TRUIR formulation, which includes parallel imaging. We have found that the analysis for the multi-coil case is significantly more complicated than the single coil case, and this is an ongoing area of research for this project.

2.3 Phase Encode Sampling Strategies

Because the data in most dynamic MR acquisitions is severly undersampled, the quality of most dynamic reconstruction schemes is heavily dependent on which k-space locations are sampled. We expect this to hold true for our TRUIR as well. We are in the process of exploring a variety of 2D phase encode (PE) sampling strategies to determine which have optimal temporal/ spatial resolution tradeoff for the TRUIR method.

The TRUIR formulation gives us some flexibility in terms of what we consider to be one time frame. An acquired set of data can be grouped in different ways to produce different reconstructed image sequences. That is, with a given amount of collected data, one can decide during post processing how many image frames one would like to reconstruct. For a given amount of data, reconstructing more frames means there is less data grouped in each frame. Traditionally, this would result in severe undersampling artifacts in the resultant image sequence, but because the TRUIR formulation includes an explicit temporal roughness penalty that enforces some connectivity between time frames, there is potential to have flexibility in the number of reconstructed frames (equivalently, frame rate), while maintaining image quality.

To date, our focus has been on two phase encode sampling strategies. First, we are looking at the sampling pattern that is currently in use on our clinical scanner. We will refer to this as the original pattern. This is an elliptically shuttered, partial Fourier pattern that is

undersampled in the ky direction by a factor of 2, where samples fall on a cartesian grid and are acquired starting at DC and then gradually moving out to the higher frequencies. The full PE sampling pattern is shown in Fig. 1, where the order in which the samples are acquired is indicated by the darkness of the circle. The darker circles represent locations that are sampled earlier in the scan and ligher circles are locations that are sampled later, i.e., the overall sampling occurs from low frequency to high frequency. For the current reconstuction method used by the clinical scanner, the pattern shown in Fig. 1 is collected for each reconstructed frame.

The second sampling pattern we are looking at is composed of the same sample locations as the original one, but acquired in a different order. Our reordering scheme is based on the premise of approximately uniformly sampling (in time) the higher and lower frequencies in the original sampling pattern. One implementation of the reordered sampling scheme is show in Fig. 2, where again the darker circles are earlier samples and lighter circles are later samples.

Figure 3 shows another comparison of the two PE trajectories. The PE locations sampled during the first half of a full acquisition are shown for the original trajectory (left), and the reordered ("new") trajectory (right). During the first half of acquisition, the original trajectory covers only the low frequencies, while the reordered trajectory covers the entire range of frequencies of a full acquisition. This is true not only for the half frame case, but for any temporally adjacent subset of samples. For a given time period, a subset of samples acquired according to the reordered trajectory will cover a wider range of spatial frequencies than those acquired with the originally ordered trajectory. Results from image reconstructions using both of these sampling patterns are presented in conjunction kinetic parameter estimates in Section 2.4.

As this project continues, we plan to explore other PE acquisition patterns and orderings, and to evaluate the resulting reconstructed image sequences. In all PE sampling schemes, we will maintain the same number of samples as the original sampling pattern, but will examine various trajectories such as variable density trajectories, pseudo-random trajectories (e.g. Poisson disc sampling), as well as trajectories that sample higher frequency locations that are outside the range of the current PE sample pattern.

2.4 Kinetic Parameters

In dynamic contrast-enhanced (DCE) MRI, a contrast agent is used to enhance the MR images. The uptake of contrast agent in tissue has been shown to be clinically important in detection and diagnosis of breast cancer, as well as other cancers. The contrast agent is injected into the subject's blood stream and as it travels through the body, it affects the underlying physical mechanisms of MRI and thereby alters the appearance of various tissues in the MR image [6–9]. The enhancement characteristics of tumors differ from those of healthy tissue; enhancement characteristics also differ between healthy and benign lesions. These differences in enhancement arise from differences in vascular permeability as well as differing angiogenic properties [10].

Standard parameters are used to measure the kinetics of DCE-MRI, including the volume transfer constant, K^{Trans}, and the rate constant, k_{ep}, [11]. One of the aims of this project is

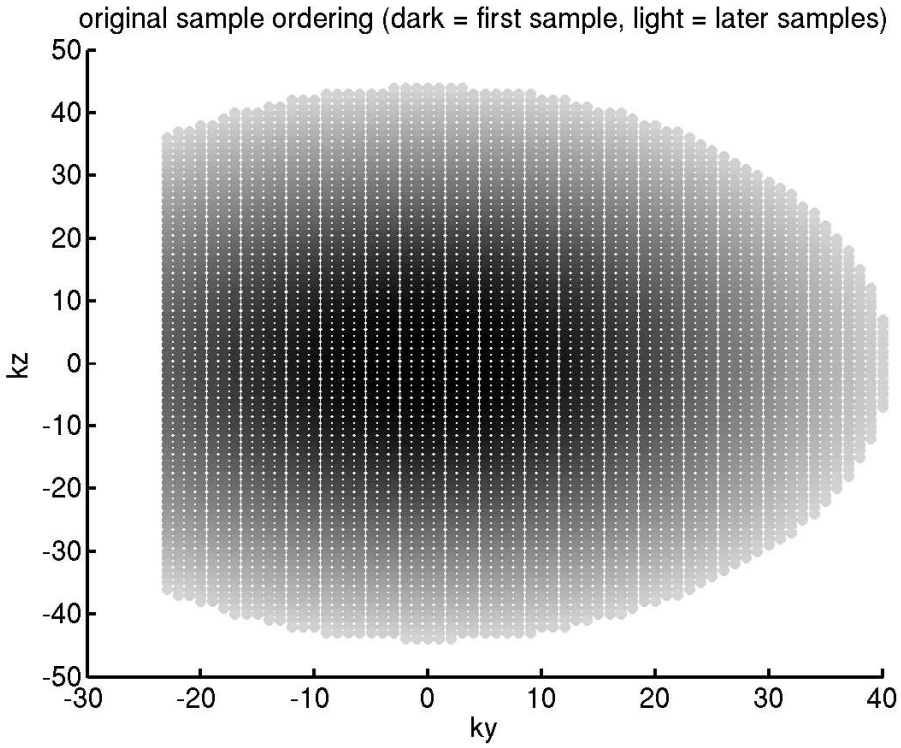

Figure 1: Phase encode sample locations and order of the original k-space trajectory, which is currently in clinical use. Darker circles represent frequency locations that are sampled earlier in the scan, while light circles represent locations sample later during the scan.

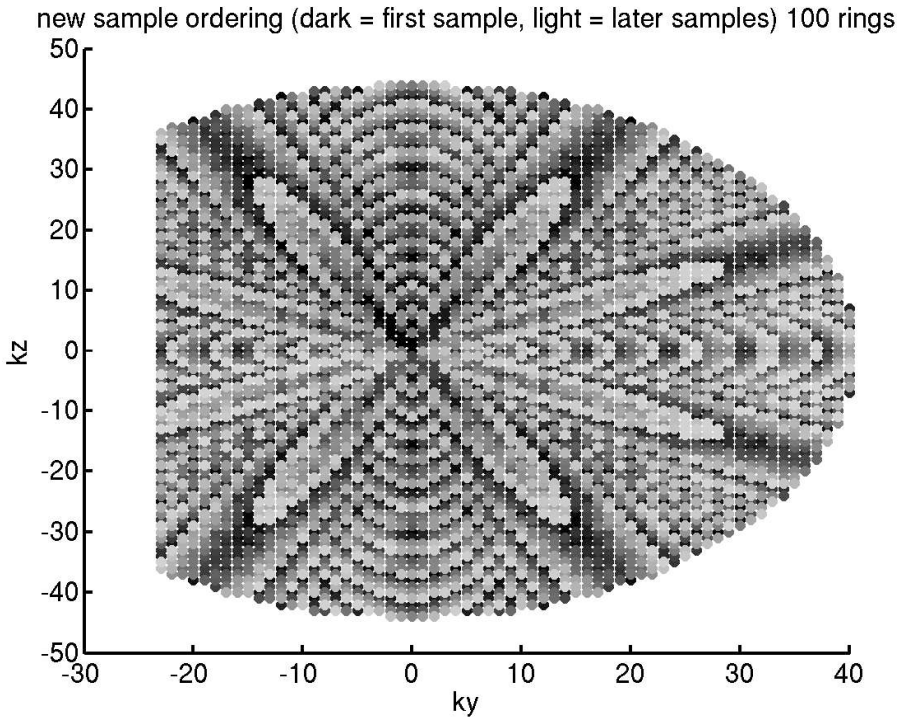

Figure 2: Phase encode sample locations and order of our reordered k-space trajectory. Darker circles represent frequency locations that are sampled earlier in the scan, while light circles represent locations sample later during the scan. The sampled frequencies are the same as those in Fig. 1, but the order in which they are sampled has been revised.

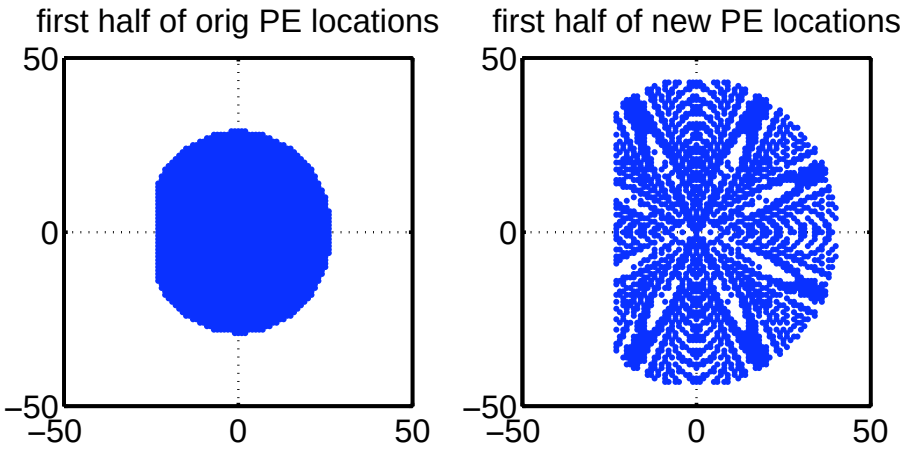

Figure 3: Phase encode sample locations that are acquired during the first half of the original trajectory (left), and the first half of the reordered trajectory (right). For a given time period, a subset of samples from the reordered trajectory covers a wider range of spatial frequencies than the original trajectory.

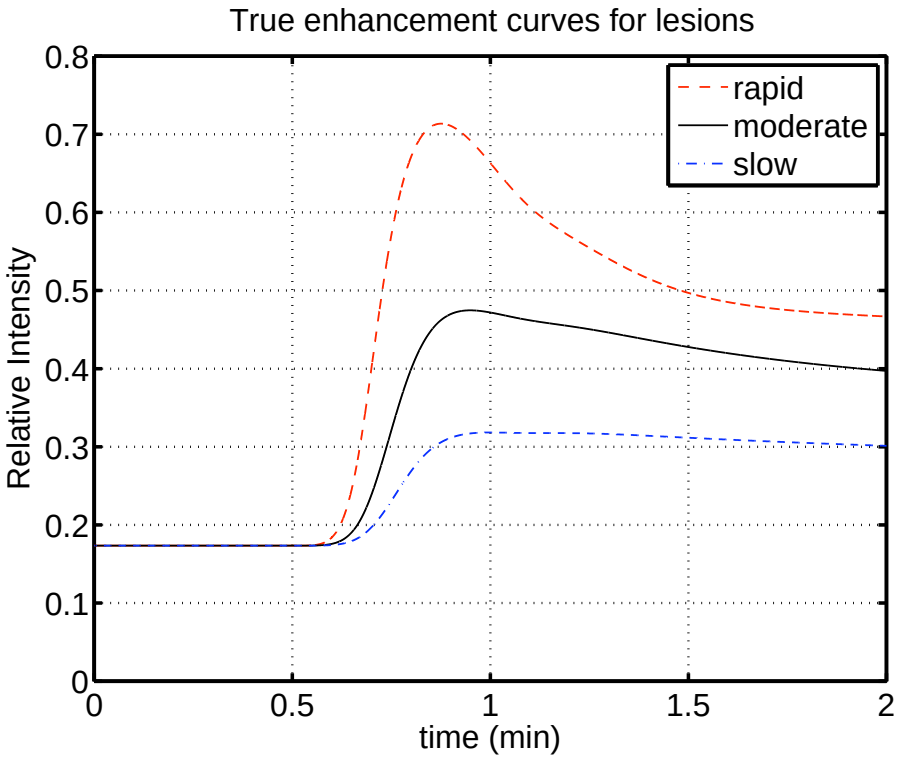

Figure 4: True enhancement curves used in our simulations of slow, moderate and rapidly enhancing lesions.

to evaluate the utility of our reconstructed image sequences to provide accurate estimates of these clinically important kinetic parameters, and this has been a focus of this year's work.

We performed simulations based on digital phantoms to examine the kinetic parameters estimated from a TRUIR reconstructed image sequence compared to kinetic estimates based on a traditional frame-by-frame (homodyne + SENSE) reconstruction method [2, 12]. The digital phantom included three "lesions", representing slow, moderate, and rapidly enhancing lesions. We used realistic enhancement curves for the lesions, which we computed using mathematical models that represent the underlying physiological processes [11, 13], as well as unique kinetic parameters for each lesion. The modeled enhancement curves for the three lesions are shown in Figure 4.

We also compared reconstructions using the original PE trajectory to those using the reordered trajectory outlined in Section 2.3. Representative reconstructions are shown in Figures 5 and 6. Figure 5 shows a traditional frame-by-frame reconstruction of the data using the original PE order. We simulated 12 frames of the full k-space trajectory, therefore the traditional reconstruction yields 12 frames as well. Figure 6 shows a 24-frame TRUIR reconstruction of data collected using the reordered PE sampling pattern. Due to the flexibility in the TRUIR formulation, we are able to reconstruct 24 image frames from the same amount of data required for a 12 frame traditional reconstruction, without much loss of image quality.

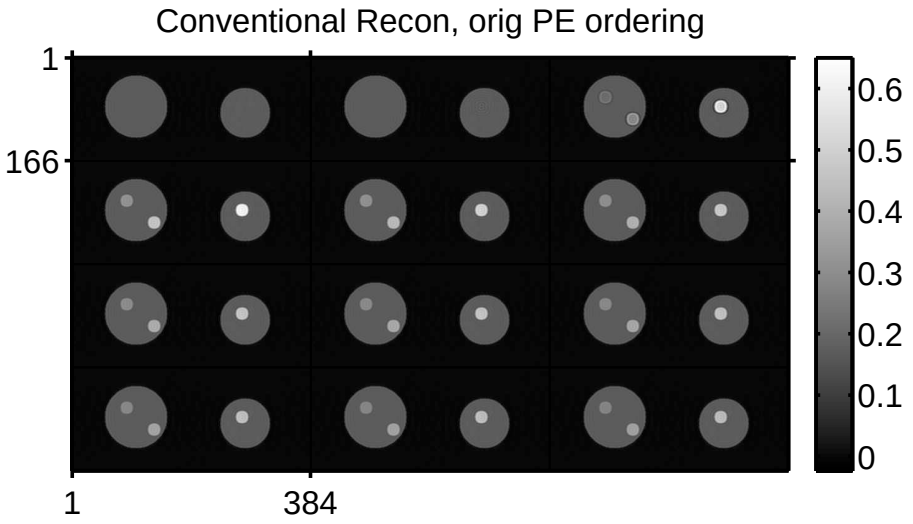

Figure 5: Traditional frame-by-frame reconstruction of the dynamic digital phantom, using the original PE sampling order.

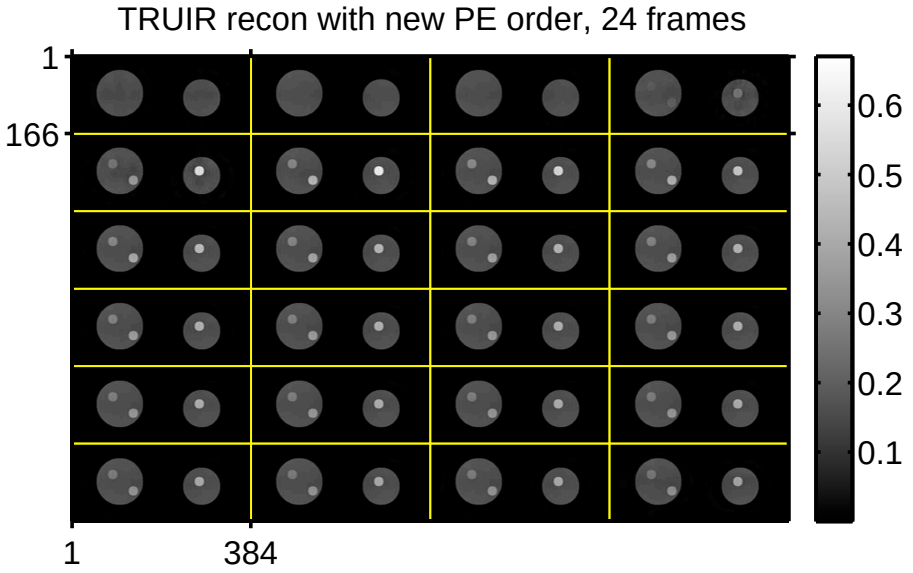

Figure 6: TRUIR reconstruction of the dynamic digital phantom, using the reordered PE sampling scheme.

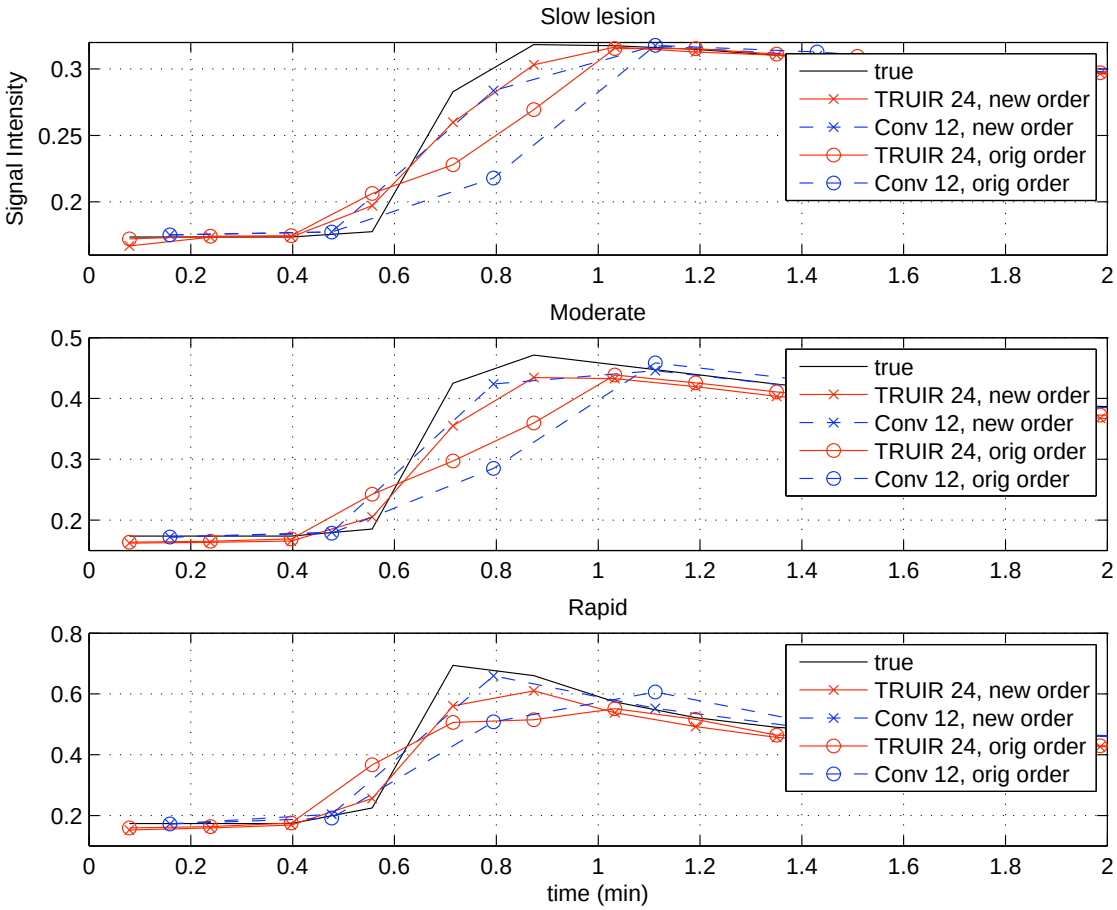

Figure 7: Enhancement curves derived from image sequences reconstructed using traditional/conventional ("conv") and TRUIR reconstruction, and the original and reordered ("new") PE sampling schemes. Top: slowly enhancing lesion. Middle: moderately enhancing lesion. Bottow: rapidly enhancing lesion. For all three lesion types, the reordered PE scheme yielded more accurate enhancement curves, both for traditional reconstruction and TRUIR.

Figure 7 shows enhancement curves measured from conventional and TRUIR reconstructions, using both the original PE order as well as the reordered PE locations ("new" in the figure caption). The true (simulated) value of the signal intensity is show as well, for reference. For all three types of lesions, the reordered PE scheme yielded more accurate enhancement curves, both for traditional reconstruction and TRUIR. Enhancement curves from traditional and TRUIR reconstructions which both used the reordered PE scheme did not differ significantly in this instance.

As discussed in Section 2.4, TRUIR reconstructions are highly dependent on the regularization parameters, particularly the temporal regularization parameter, α. We completed TRUIR reconstructions over a wide range of values for α (from $\log_2 \alpha = -10$ to $\log_2 \alpha = 20$), and then computed the kinetic parameters for each lesion based on these reconstructions [6–9, 11, 14].

As expected, the estimated values for K^{Trans} and k_{ep} varied immensely over the range of α, as can be seen in Figure 8. This figure shows the percent error in the estimates of the the rate constant, k_{ep}, and the transfer constant, K^{Trans}, vs α for 12-frame traditional reconstructions using both the original and new PE order, and 24-frame TRUIR reconstructions using both PE ordering schemes. The left column of plots show the percent error in estimates of the rate constant, k_{ep}, for the slow (top), moderate (middle), and rapidly enhancing lesion (bottom). The the right column of plots show the percent error in estimates of the transfer constant, K^{Trans}, for the slow (top), moderate (middle), and rapidly enhancing lesion (bottom). The percent error for the conventional reconstruction methods is a flat line since this frame-by-frame method does not depend on α. While the results are far from conclusive, we can see that using a TRUIR temporal regularization parameter value of $\sim 2^{10}$ yielded the best overall results for kinetic parameter estimation in this study.

2.5 Deviations from Original Statement of Work

Our original project proposal included validating TRUIR on real patient data that has been collected as part of a different study at our institution. Unfortunately, we have since discovered that the data collected during that study does not include all of the necessary data for us to perform our own reconstructions. Specifically, scan-specific sensitivity maps are required for reconstruction of multi-coil data, but the baseline data required to compute these maps has not been saved, as it was not needed for the other study. In the absense of available patient data, but still wanting to show results using real data from the scanner, we now plan to evaluate TRUIR by conducting MR experiments collecting real scanner data from a physical dynamic phantom.

3 Key Research and Training Accomplishments

- Continued investigation of choice of algorithms' regularization parameters based on desired spatial and temporal resolution.
- Explored 2D phase encode sampling strategies to determine how sampling patterns affect TRUIR reconstructions, and to validate the flexibility of the TRUIR formulation.
- Implemented realistic simulations using mathematical models that relate enhancements in MR images to the underlying physiological behavior of both healthy and diseased tissues.
- Computed kinetic parameters of tissue types from TRUIR reconstructed image sequences and compared to traditional reconstructions.
- PI earned certification from the University's Program for Education and Evaluation in Responsible Research and Scholarship (PEERRS) during this award period.

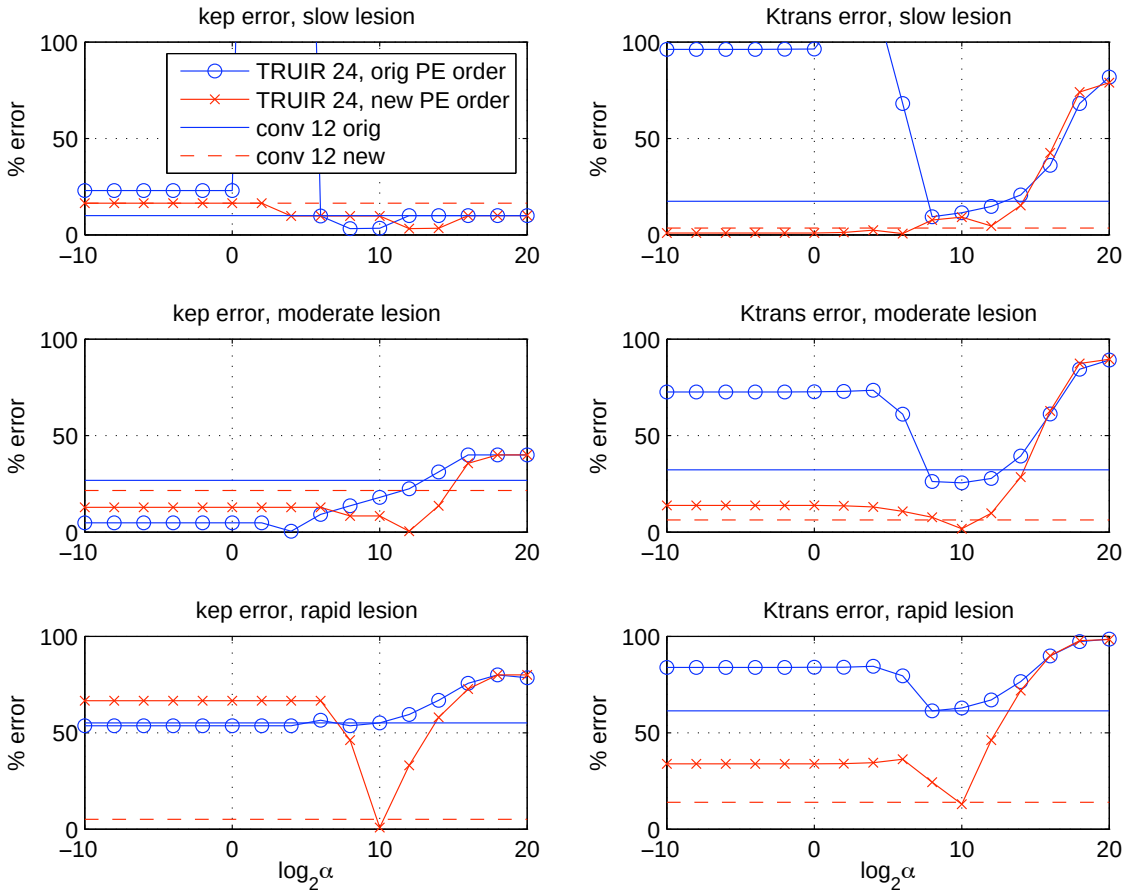

Figure 8: Kinetic estimates derived from image sequences reconstructed using traditional/conventional ("conv") and TRUIR reconstructions, and the original and reordered ("new") PE sampling schemes. Left column shows the percent error in k_{ep} estimates vs the temporal regularization parameter, α. The right column shows the percent error in K^{Trans} estimates vs α. Top row is for the slow lesion, middle row for moderate lesion and bottom row for the rapidly enhancing lesion.

4 Reportable Outcomes

- Created new data objects to assist in TRUIR reconstruction. Added many tools and functions to code base, for use by current and future students and researchers.

5 Conclusion

Dynamic constrast-enhanced MRI studies demand both high spatial and high temporal resolution. We want high spatial resolution to visualize morphology and we want high temporal resolution to accurately follow the tracer kinetics of the tissue.

We have developed a reconstruction scheme based on an image domain model that does not attempt any data domain recovery, but rather explicitly uses the assumption of temporal smoothness in the image domain to estimate the image sequence that best fits the available data. We continue to investigate resolution-based approaches for choosing the regularization parameters required by our algorithms. We are exploring a variety of 2D k-space sampling trajectories to determine which may provide better spatiotemporal resolution with TRUIR, and have presented some representative results of our studies to date. We have implemented a method of accurately simulating tissue enhancement based on kinetic parameters and the underlying tissue physiology, and have used the same mathematical models to derive kinetic parameter estimates from dynamic image sequences. Overall the TRUIR method has shown promising results, although there are still many open questions that remain to be answered.

References

[1] D. K. Sodickson and W. J. Manning, "Simultaneous acquisition of spatial harmonics (SMASH): Fast imaging with radiofrequency coil arrays," *Mag. Res. Med.*, vol. 38, no. 4, pp. 591–603, Oct. 1997.

[2] K. P. Pruessmann, M. Weiger, M. B. Scheidegger, and P. Boesiger, "SENSE: sensitivity encoding for fast MRI," *Mag. Res. Med.*, vol. 42, no. 5, pp. 952–62, Nov. 1999.

[3] M. Bydder, J. Perthen, and J. Du, "Optimization of sensitivity encoding with arbitrary k-space trajectories," *Mag. Res. Im.*, vol. 25, no. 8, pp. 1123–9, Oct. 2007.

[4] K. A. Khalsa and J. A. Fessler, "Resolution properties in regularized dynamic MRI reconstruction," in *Proc. IEEE Intl. Symp. Biomed. Imag.*, 2007, pp. 456–9.

[5] J. A. Fessler and W. L. Rogers, "Spatial resolution properties of penalized-likelihood image reconstruction methods: Space-invariant tomographs," *IEEE Trans. Im. Proc.*, vol. 5, no. 9, pp. 1346–58, Sept. 1996.

[6] E. M. Haacke, R. W. Brown, M. R. Thompson, and R. Venkatesan, *Magnetic resonance imaging: Physical principles and sequence design*, Wiley, New York, 1999.

[7] P. S. Tofts and A. G. Kermode, "Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts," *Mag. Res. Med.*, vol. 17, no. 2, pp. 357–67, Feb. 1991.

[8] M. Sasaki, E. Shibata, Y. Kanbara, and S. Ehara, "Enhancement effects and relaxivities of gadolinium-DTPA at 1.5 versus 3 Tesla: A phantom study," *Magnetic Resonance in Medical Sciences*, vol. 4, no. 3, pp. 145–9, 2005.

[9] R. Rakow-Penner, B. Daniel, H. Yu, A. Sawyer-Glover, and G. H. Glover, "Relaxation times of breast tissue at 1.5T and 3T measured using IDEAL," *J. Mag. Res. Im.*, vol. 23, no. 1, pp. 87–91, Jan. 2006.

[10] M. V. Knopp, E. Weiss, H. P. Sinn, J. Mattern, H. Junkermann, J. Radeleff, A. Magener, G. Brix, S. Delorme, I. Zuna, and G. . Kaick, "Pathophysiologic basis of contrast enhancement in breast tumors," *J. Mag. Res. Im.*, vol. 10, no. 3, pp. 260–6, Sept. 1999.

[11] P. S. Tofts, G. Brix, D. L. Buckley, J. L. Evelhoch, E. Henderson, M. V. Knopp, H. B. Larsson, T. Y. Lee, N. A. Mayr, G. J. Parker, R. E. Port, J. Taylor, and R. M. Weisskoff, "Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols," *J. Mag. Res. Im.*, vol. 10, no. 3, pp. 223–32, Sept. 1999.

[12] D. C. Noll, D. G. Nishimura, and A. Macovski, "Homodyne detection in magnetic resonance imaging," *IEEE Trans. Med. Imag.*, vol. 10, no. 2, pp. 154–63, June 1991.

[13] C. Yang, G. S. Karczmar, M. Medved, and W. M. Stadler, "Multiple reference tissue method for contrast agent arterial input function estimation," *Mag. Res. Med.*, vol. 58, no. 6, pp. 1266–75, Dec. 2007.

[14] G. Golub and V. Pereyra, "Separable nonlinear least squares: the variable projection method and its applications," *Inverse Prob.*, vol. 19, no. 2, pp. R1–26, Apr. 2003.